PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	23.07.2004
Applicant's or agent's file reference: FPAA335PCT	**REPLY DUE** within 3 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN 03/00289	27.08.2003	28.08.2002

International Patent Classification (IPC) or both national classification and IPC
A61K35/78

Applicant
LUPIN LTD. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 28.12.2004

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-29 as originally filed

Claims, Numbers

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 19

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 19 (directed to a method of treatment)

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19
Inventive step (IS)	Claims	1-19
Industrial applicability (IA)	Claims	1-19

2. Citations and explanations

see separate sheet

ad section III:

1). Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

ad section V:

1). The present application concerns an anticonvulsant composition comprising an extract of the pericarp of the fruit of S. trifoliatus, comprising from 0.001 to 1.0 (% w/v) of hederagenin and pharmaceutically acceptable carriers (claims 1-11). Moreover, the present application also concerns a process for preparing an extract containing 4 to 8% (w/w) of hederagenin (claims 12-14), a process for preparing an anticonvulsant composition (claim 15), an extract according to claims 1 and 12 (claims 16-18) and the use of said composition for the treatment of migraine (claim 19).

2). For the assessment of the present claim 19 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The same applies to the corresponding passages throughout the description referring to a method of treatment of the animal/human body (cf. pp. 1 and 13ff).

3). With regard to the present subject-matter the following documents have been retrieved and will be discussed as follows:

D1, Pharmacol. Res. Comm., 8(2), 1976, pp. 199-210, Chaturvedi A.K., et al., studies the anti-inflammatory and anticonvulsive properties of some natural plant triterpenoids, explicitly referring to hederagenin (cf. abstract, summary and

introductive part on page 200, 2nd para. bridging with page 3, first para.9, page 202, fig. 1, page 207, first para.). On page 203, lines 1-6, a concentration of 0.25% (w/v) is administered in anticonvulsant determination assays. Although no explicit mention is made on the extraction of the pericarp of S. trifoliatus, the hederagenin concentration of D1 clearly falls into the ambit of the present claim 1.

D2, EP-A-767 177, discloses the use of the triterpenoid derivatives of the hederagenin family in the therapy of nephritis (cf. abstract, page 2, line 41 bridging with page 3, line 7, page 11, lines 24-30). Moreover, preparations containing an extract of the pericarp of S. mukurossi according to reference example 1 are administered as pharmaceutical composition containing 0.1-99.5% of hederagenin in a "medicinally acceptable nontoxic, inert carrier (cf. page 11, lines 28-30). As such the teaching of D2 clearly falls into the scope of claim 1 as presently on file.

D3, Patent Abstracts of Japan, 015(012) (C-0795), jan. 1991 & JP 02 262510 (Inabata Koryo KK), 25/10/1990, discloses a dentifrice composition for preventing inflammation of the gum of periodontitis, said composition comprising an extract of hederagenin extracted from the pericarp of S. mukurossi (cf. abstract). The teaching of D3, however, is silent on the exact content of hederagenin within said dentifrice composition.

D4, Chem. Pharm. Bull. 20(9), July 1972, pp. 1935-1939, Higuchi R. et al., reports on the isolation of several triterpenoid saponins, including hederagenin 3-O-glycosides from the seeds of Akebia quinata (cf. summary and lines 1-17 on page 1935). No reference to an exact hederagenin concentration is given in D4.

D5, Chemical and Pharmaceutical Bull., 49(9), sep. 2001, pp. 1195-1197, Kanchanapoom T. et al., reports on the isolation of three new acetylated triterpene saponins from the pericarp of S. emarginatus. The use of the pericarps in Thai traditional medicine as antipruritic, as a natural surfactant and antifertility agent are mentioned as well (cf. abstract and introduction on page 1195, left-sided col.). D5, however, is silent on a composition comprising an extract containing hederagenin in the concentration as depicted in claim 1.

4). General statements in the description trying to extend the scope of protection in an ambiguous and uncleary way (cf. 27 "non-limiting") should be avoided.